REMARKS

I. Amendments

Specification: The specification has been amended at page 8 in order to clarify that the sequence disclosed in Figures 3A-3B is the LRP5 gene sequence disclosed in SEQ ID NO:1, also illustrated in Figure 1, and that the sequence continues from Figure 3A to 3B. The specification has further been amended at page 50, merely in order to correct typographical errors that were pointed out by the Examiner in the instant Office Action. More particularly, the term "regeneration" was mistakenly used where the term "degeneration" was intended.

The amendments to the specification do not add or constitute new matter, and are completely supported by the specification and originally filed claims and figures.

Claims: Claims 5-12 are canceled, and new claims 17-25 are added. Claims 1-4 and 13-16 have been withdrawn from consideration. The newly added claims do not constitute new matter and are completely supported throughout the specification and originally filed claims. More particularly, newly added claims 17-25, drawn to a transgenic mouse whose genome comprises a disruption in a low density lipoprotein related protein 5 gene and a method of producing said mouse can be found, for example, at page 8, line 17 through page 15, line 3, and at page 50, line 1 through page 51, line 8, of the specification.

The foregoing amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. The Applicant reserves the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Upon entry of the amendment, claims 17-25 are pending in the instant application.

II. Claim Objections

Claim 10 has been objected to by the Examiner because it is dependent upon claim 1, which is no longer under consideration. The Applicant has canceled claim 10, rendering this objection moot.

III. Sequence Compliance

The Examiner has contended that the instant application fails to comply with the requirements of 37 C.F.R. 1.821 through 1.825 in that the sequence in Figure 3A does not have a sequence identifier. The Applicant has amended the specification at the Brief Description of the Drawings in order to clarify that the sequence disclosed in Figures 3A to 3B is one continuous sequence (the LRP5 gene disclosed in SEQ ID NO:1).

The Sequence Listing submitted on July 1, 2002 (originally submitted December 19, 2001), in computer readable format (CRF) and paper, contains all sequences disclosed in the application. Therefore, the Applicant believes that a substitute Sequence Listing in CRF is not required. Moreover, the content of the paper and computer readable copies of the Sequence Listing submitted on July 1, 2002 are identical. The sequence listing submitted in this application merely presents nucleotide and/or amino acid sequences that appeared in the application as originally filed in accordance with 37 C.F.R. §1.821-1.825, thus no new matter has been introduced into the application.

IV Rejections

A. Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 5-12 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Specifically, the Examiner asserts that the specification, while enabling for a transgenic mouse whose genome comprises a homozygous disruption of LRP5, wherein said mouse lacks functional LRP5 and has a phenotype of retinal degeneration, and a method of making the mouse, and a cell whose genome comprises a homozygous disruption of LRP5 isolated from the transgenic mouse, is not enabling for any animal, LRP5 gene, phenotype, cell, disruption, or method of making or using the transgenic mouse as claimed.

The Applicant respectfully traverses the rejection. However, the Applicant has cancelled claims 5-12.

New claims 17-25 are drawn to a transgenic mouse, a method of making the mouse and a cell obtained therefrom, whose genome comprises a homozygous disruption in a LRP5 gene, which mouse lacks functional LRP5 and exhibits a specific phenotype disclosed in the application, and more particularly, a phenotype of retinal degeneration, increased anxiety or

hypoactivity. The Applicant contends that new claims 17-25 are fully enabled by the instant specification. In particular, the Applicant has described the transgenic mouse, cells and methods as claimed in the new claims 17-25 so that one skilled in the art would be apprised of how to make and use the transgenic mouse and cells and tissues as claimed. A skilled artisan would be well apprised of how to determine the phenotype of such a transgenic mouse, and, in particular, how to test for anxiety and/or hypoactivity phenotypes using the open field test.

In view of the cancellation of claims 5-12, and the submission of new claims 17-25, which are completely enabled by the specification as originally filed, the rejection under 35 U.S.C. § 112, first paragraph, is no longer relevant. Therefore, the Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

B. Rejection under 35 U.S.C. § 102

Claims 5-12 were rejected under 35 U.S.C. § 102(b) as being anticipated by Rohlmann (1998, *J Clin Invest,* Vol 101, pg 689-695, "Rohlmann"). The Applicant respectfully traverses the rejection. However, in light of the cancellation of claims 5-12, the rejection under 35 U.S.C. § 102 is no longer relevant.

The Applicant submits that new claims 17-25 are not anticipated by Rohlmann. More particularly, new claims 17-25 are drawn to a transgenic mouse whose genome comprises a homozygous disruption in a LRP5 gene, which mouse lacks functional expression of LRP5 and exhibits a specific phenotype, namely retinal degeneration, increased anxiety or hypoactivity. The claims are further drawn to cells obtained from the transgenic mouse and methods of making the transgenic mouse. Rohlmann fails to teach the invention as recited in claims 17-25.

According to the Examiner, Rohlmann teaches making a transgenic mouse having a disruption in LRP using ES cells. The Examiner contends that the disclosure of Rohlmann allegedly encompasses disruption of the LRP5 gene as claimed by the instant invention. However, the Applicant argues that the disclosure of Rohlmann does not teach all of the limitations recited in current claims 17-25, and in particular does not recite the phenotype of a transgenic mouse whose genome comprises a disruption in an LRP5 gene as defined by the instant specification. More particularly, Rohlmann does not teach the disruption in the LRP5 gene in the transgenic mouse, and further does not disclose the transgenic mouse exhibiting a phenotype of retinal degeneration, increased anxiety or hypoactivity.

As the rejection under 35 U.S.C. § 102(b) is no longer relevant as a result of the cancellation of claims 5-12, and new claims 17-25 are not anticipated by the disclosure of Rohlmann as stated above, Applicant requests withdrawal of the rejection.

C. Rejection under 35 U.S.C. § 103

Claims 5-12 were rejected under 35 U.S.C. § 103 (a) as being unpatentable over Rohlmann, 1998, *J Clin Invest,* 101: 689-695 ("Rohlmann") in view of Hey, 1998, *Gene*, 216: 103-111 ("Hey"). The Applicant respectfully traverses this rejection. However, in view of the cancellation of claims 5-12, the rejection under 35 U.S.C. § 103 is no longer relevant.

The Applicant submits that new claims 17-25 are non-obvious over the teachings of the prior art references. More particularly, the claimed invention relates to the *in vivo* mammalian characterization of the function of the LRP5 gene, and provides transgenic mice and cells, the genomes of which comprise disruptions in the endogenous LRP5 gene, and methods of making the mice, all of which are not obvious in view of the sole or combined teachings and disclosures of the references cited by the Examiner.

According to the Examiner, Rohlmann discloses making a transgenic mouse having a disruption in LRP made using ES cells. The Examiner states that Rohlmann does not disclose the LRP gene was LRP5.

Hey, as characterized by the Examiner, merely discloses the nucleic acid sequence of the mouse LRP5 gene.

In order to establish a *prima facie* case of obviousness, the Examiner must meet three basic criteria: there must be some suggestion or motivation to modify a primary reference or combine reference teachings; there must be a reasonable expectation of success; and the prior art reference(s) must teach or suggest all the claim limitations. See MPEP §2143. The Applicant contends that the prior art references cited by the Examiner are not sufficient to establish a *prima facie* case of obviousness.

The Examiner asserts that the ordinary artisan would have been motivated to combine the teachings of the prior art references to determine the role of the LRP5 gene in liver because Hey allegedly disclosed that LRP5 is expressed in the liver. The Applicant respectfully disagrees. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. See MPEP 2143.01. However, claims 5-12 have been canceled. The Applicant submits that neither

Rohlmann nor Hey suggest the desirability of disrupting the LRP5 gene in a mouse as presently recited in claims 17-25. Therefore, the Examiner has failed to provide sufficient evidence in the prior art references of the motivation or suggestion to combine the prior art references required to establish a case of *prima facie* obviousness.

Further, the Applicant submits that the Examiner has failed to show that one of ordinary skill in the art would have a reasonable expectation of success to make a LRP5 knockout mouse based on the combined disclosures of the prior art references, and in particular, based on the disclosure of Rohlmann, who discloses a transgenic mouse comprising a LRP gene disruption, and Hey, who provides the sequence for the LRP5 gene. However, Rohlmann does not teach, suggest or contain any disclosure regarding the LPR5 gene as defined and claimed in the instant invention by the Applicant. More particularly, Rohlmann does not disclose or suggest any characterization of the phenotype observed in the transgenic mouse whose genome comprises a disruption in LRP5 as claimed by the Applicant. That Hey merely provides the sequence of the LRP5 gene does not cure that failing. In any case, the Applicant has cancelled claims 5-12, and submits that one of ordinary skill in the art would not have a reasonable expectation of success in combining the cited references to create the invention as recited in new claims 17-25.

Finally, in order to establish a *prima facie* case of obviousness, the Examiner must also show that the prior art references teach or suggest all of the claimed limitations. As described above, the disclosure of Rohlmann is limited to a transgenic mouse having a disruption in an LRP gene. Hey is limited to providing disclosure related to the nucleic acid sequence of the LRP5 gene in particular.

However, neither Rohlmann nor Hey, alone or in combination, teaches all of the limitations as presently claimed in claims 17-25. As acknowledged by the Examiner, Rohlmann provides no disclosure or teaching of how to make a transgenic mouse comprising a disruption in a LRP5 gene described in the instant specification, and in particular does not disclose a specific phenotype of the transgenic mouse, particularly a phenotype of a retinal degeneration, increased anxiety or hypoactivity, as claimed by the present invention. Likewise, Hey does not provide any teaching or suggestion relating to targeted disruptions in any gene, particularly in a LRP5 gene. More particularly, the disclosure of Hey fails to provide any teaching or suggestion that relates to the transgenic mice and cells as recited in the pending claims.

Taken together, the disclosures Rohlmann and Hey are devoid of any teaching or suggestion of the transgenic mice and cells as recited in the pending claims. More particularly, the disclosures of Rohlmann and Hey, alone or combined, do not teach or suggest in any way transgenic mice comprising disrupted LRP5 genes, wherein such transgenic mice exhibit a phenotype, and in particular exhibit a phenotype of retinal degeneration, increased anxiety or hypoactivity. Further, these prior art references do not disclose the tissues and cells comprising the disrupted LRP5 gene as claimed by the present invention.

As the obviousness rejection is no longer relevant as result of the cancellation of claims 5-12, and new claims 17-25 are not obvious in view of the teachings of Rohlmann and Hey, the Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 103.

It is believed that the claims are currently in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-193.

Respectfully submitted,

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